In the Claims:

Please cancel claims 1-16, 19 and 22 without prejudice.

REMARKS

Claims 1-23 are in this case. Claims 1-16, 19 and 22 have been withdrawn from consideration by the Examiner. Claims 17, 18, 20, 21 and 23 have been rejected. Claims 1-16, 19 and 22 have been canceled without prejudice.

Objection to the Specification

The Examiner has objected to the specification for failing to include a specific reference to the earlier filed application in the text. Applicant has now amended the text to include such a reference as the first sentence of the specification, as a separate paragraph. Applicant has provided a marked-up version of page 1 of the specification, which includes this amendment. Applicant feels that this overcomes the objection of the Examiner in this regard.

Rejections over 35 USC 112

The Examiner has rejected claims 21 and 23 under 35 USC 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention, because of the use of the term "substantially prevent". The rejections of the Examiner are respectfully traversed.

The term "substantially prevent", as used in claims 21 and 23, refers to the ability of Halofuginone and other quinazolinone derivatives to prevent the occurrence of cardiac fibrosis. The qualifier "substantially" refers to any type of prevention of cardiac fibrosis, regardless of whether absolute and complete prevention is achieved. This point is important because Halofuginone was shown in the instant specification to be clearly effective for preventing cardiac fibrosis, even if absolute and complete inhibition of all molecular processes contributing toward cardiac fibrosis was not shown. For example, rats given both Halofuginone and angiotensin II showed a substantial reduction in rat collagen α1(I) gene expression, particularly when compared to the level seen in rats receiving only angiotensin II. Although the angiotensin II - mediated increase in gene expression was not completely abolished by Halofuginone, both gross and fine morphological changes caused by angiotensin II did not appear in rats treated with Halofuginone (page 27, lines 3-32, and also Figure 7). Thus, the term "substantially preventing" clearly refers to at least a partial inhibition of the pathological processes of cardiac fibrosis.

Rejections over 35 USC 102(b)

The Examiner has rejected claims 17-18, 20-21 and 23 under 35 USC 102(b) as being anticipated by Pines et al. (US Patent No. 5,449,678; hereinafter referred to as the "Pines '678"). The rejections of the Examiner are respectfully traversed.

The Examiner states that Pines '678 teaches the use of quinazolinone containing compositions (eg, halofuginone) for treating or preventing fibrotic

disorders such as myocardial fibrosis by inhibiting collagen type I synthesis (col 6, line 4).

Applicant asserts that the disclosure of Pines '678, and in particular the line singled out by the Examiner, does not disclose the specific features of the currently claimed invention, as disclosed and taught in the present application.

The present application relates to the prevention and/or treatment of cardiac fibrosis by the administration of quinazolinone derivatives such as Halofuginone, as well as pharmaceutical compositions for the administration of such of quinazolinone derivatives to a patient. The specification, in particular Example 5, clearly demonstrates the efficacy of Halofuginone *in vivo* for the inhibition of the pathological processes of cardiac fibrosis, and hence for both the treatment and prevention of cardiac fibrosis. The specification describes a large number of different mechanisms which may be responsible for the *in vivo* efficacy of Halofuginone and related compounds, including inhibition of collagen α1(I) gene expression and hence reduction in collagen type I synthesis; inhibition of collagenase type IV production; inhibition of H19 gene expression; decreasing the release of cytokines IL-1β and TNFα; overall regulation of ECM (extracellular matrix) deposition and remodeling; and inhibition of integrin expression. Thus, inhibition of collagen type I synthesis is only one of many different potential targets of Halofuginone for treating and/or preventing cardiac fibrosis. In any case, cardiac fibrosis is characterized by high levels of deposition of many different ECM components, and not only by collagen type I deposition.

The demonstration of the efficacy of Halofuginone for the treatment and/or prevention of cardiac fibrosis in the present application does not rely upon any particular mechanism of action, because the present application clearly shows the

efficacy of Halofuginone *in vivo*, in a rat model. For instance, Example 5, starting on page 24, describes the significant efficacy of Halofuginone in a rat model of cardiac fibrosis, in which such fibrosis is induced by angiotensin II. The data clearly show that adminstration of Halofuginone to the rats clearly inhibited the pathological processes of cardiac fibrosis, particularly with regard to gross and fine morphological changes in cardiac tissue, as shown for example in Figures 6 and 7. Therefore, Applicant has demonstrated the clear efficacy of Halofuginone for treatment and/or prevention of cardiac fibrosis.

It is important to note that both structurally and functionally, cardiac tissue is a unique tissue. Structurally, it is neither typical of striated muscle nor typical of smooth muscle but rather shares attributes of both types of muscle. Functionally, it is unique in that it must contract in a predetermined carefully orchestrated fashion in order to accomplish its function, and that even minor structural damage can impede its proper function. What might constitute a survivable level of damage or loss of functionality in almost any other tissue type (certainly in any other muscle type) can be life threatening in the case of cardiac function. Thus, the present specification demonstrates the efficacy of Halofuginone as a treatment and/or suitable preventive medicament for this highly unique tissue.

By contrast, the Pines '678 patent describes *in vitro* tissue culture experiments to determine the effect of Halofuginone on skin fibroblasts and chondrocytes, which are certainly not constituents of cardiac tissue. For instance, Example 1 describes the effect of Halofuginone on collagen type I gene expression and proline incorporation into collagenase-digestible proteins in avian *skin* fibroblasts. Example 2 describes the effect of Halofuginone on collagen synthesis and collagen α1(I) gene expression by *skin* fibroblasts and Example 3 describes the

effect of Halofuginone on *skin* collagen content in the murine chronic type of GVHD.

The Pines '678 patent certainly does not demonstrate that Halofuginone would be effective as an *in vivo* treatment for fibrotic myocardial tissue, since cardiac tissues are different from other types of tissues:

> "[The efficacy of Halofuginone as a treatment for cardiac fibrosis] is unexpected because cardiac tissue is composed of highly differentiated cells which must maintain a high overall level of organization in order to function effectively. Furthermore, myocardial tissue must contract as a single unit in response to an electrical signal, which is not a property associated with other, previously studied tissues for the treatment of fibrosis...*This property is specific to cardiac tissues*, and increases the damaging effect of fibrosis, since fibrotic tissue cannot contract in this manner. Second, damaged myocardial tissue contracts improperly...Third, *the tissue of the heart must function as a single unit. Other tissues, such as lung and liver, are composed of different tissue types and structures* which can more or less function independently" (see page 24, lines 15-29; words in brackets and emphases added).

Therefore, the Pines '678 patent is in no way predictive of any effect of Halofuginone on cardiac tissue, *in vitro* or *in vivo*.

The present application also discloses (and distinguishes) the Pines '678 patent from the present invention, as shown on page 17, lines 2-8 of the present application, which notes that the deposition of collagen had been thought to be necessary for wound strength, yet as shown in US Patent No. 5,852,024, in fact treatment with Halofuginone inhibited excessive collagen deposition but did not reduce wound strength.

Therefore, as is disclosed in the present specification, it would not be possible to predict as a generalization from experiments involving skin or any other fibroblasts (of the examples of the Pines '678 patent), whether a particular

treatment would preserve tissue function and prevent fibrosis specifically of cardiac tissue. This has been disclosed for the first time in the present invention using highly sophisticated models of cardiac functionality.

The Examiner has focused on one statement at col. 6, line 4 of the Pines '678 patent which surmises that the compositions disclosed in the patent are useful for the treatment of cardiac fibrosis, presumably due to the effect of Halofuginone on collagen synthesis. Applicant has specifically disclosed and provided an example from the Pines '678 patent that the *in vivo* effects of Halofuginone on cardiac cells cannot be predicted from an analysis of the *in vitro* effects of Halofuginone on skin cells, and further that predictions on experimental results cannot be made even when the *in vitro* and *in vivo* experiments are performed on the same types of cells.

In *In re Gandadharam*, 13 U.S.P.Q.2d 1568 (Fed. Cir. 1989), the applicant in that case appealed the decision of the Board of Patent Appeals and Interferences ("Board") upholding the Examiner's final rejection of the application under 35 USC 103. The invention disclosed the use of CQQ to treat a mammalian bacterial infection. The examiner in that case relied upon a single reference, with only *in vitro* data and co-authored by the applicant in that case, to assert that the cited reference would provide a reasonable expectation of success for effectively treating a mammal with CQQ. The Board rejected the applicant's assertion that *in vitro* results cannot be used to predict *in vivo* success,

> "The very positive *in vitro* bactericidal activity of CQQ against the above-mentioned bacteria...certainly favors the *in vivo* use of said compound in the treatment of tuberculosis in mammals". (U.S.P.Q.2d at 1568)

The Federal Circuit, in reversing the Board's decision, stated,

> "The issue presented by this appeal is *not* whether *in vitro* results can be used to predict *in vivo* success, rather it's simply whether the ...(PTO)...carried its burden of proving a prima facie case of obviousness..." (Id. at 1569; emphasis in original).
>
> "The Board's *prima facie* case amounts to the general reference [from the cited article of the applicant] of positive results that were obtained using CQQ in an entirely different context, *in vitro*, than that in which it is claimed, and precatory, encouraging statements related to uncertain future investigations and possible results." (Id. at 1569)
>
> "...simply because a drug gives positive results *in vitro*, it does not necessarily follow that there is a reasonable probability of success for therapeutic use of that drug *in vivo*...there is evidence in this record...regarding the noncorrelation of *in vivo* from *in vitro* efficacy generally and with respect to tuberculosis" (Id. at 1570).

Applicant asserts that, in the present application, similar to Gangadharam, the Examiner has not carried the burden of proving a *prima facie* case of either anticipation or of obviousness based on the hopeful prediction of treating cardiac fibrosis with Halofuginone at col. 6, line 4 of the Pines '678 patent.

In addition, unlike *Gangadharam*, the present disclosure is not simply a description of *in vivo* experiments performed according to a description of *in vitro* results from the Pines '678 patent, since Applicant is not disclosing *in vivo* experiments to study the effects of Halofuginone on diseases involving skin fibroblasts and chondrocytes. Rather, the present invention demonstrates that Halofuginone can be used effectively *in vivo* to treat or prevent cardiac fibrosis. As previously described, such an effective use is clearly patentable, since both structurally and functionally, cardiac tissue is a unique tissue. Structurally, it is neither typical of striated muscle nor typical of smooth muscle but rather shares attributes of both types of muscle. Functionally, it is unique in that it must contract

in a predetermined carefully orchestrated fashion in order to accomplish its function, and that even minor structural damage can impede its proper function. Thus, the present specification demonstrates the efficacy of Halofuginone as a treatment and/or suitable preventive medicament for this highly unique tissue.

In any case, the Pines '678 patent does not teach or suggest any use of Halofuginone for the prevention of cardiac fibrosis, since the statement at col. 6, line 4 of the Pines '678 patent is silent with regard to prevention.

Thus, from the above arguments, it is clear that the present claims and novel and non-obvious over the Pines '678 patent, and that furthermore a terminal disclaimer is not required. The Examiner had asserted a double patenting rejection over the Pines '678 patent, which is clearly moot for the reasons given above.

From the above remarks and amendments, Applicant feels that claims 17, 18, 20, 21 and 23 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

D'vorah Graeser
US Patent Agent
Reg. No. 40,000

Date: October 7, 2002